FOURTH ANNUAL

SPOTLIGHT ON AGING RESEARCH

MONDAY, SEPT. 9, 2013
Clinical and Translational Research Building
2004 Mowry Road

UF Institute on Aging
UNIVERSITY of FLORIDA
PROGRAM

3-4 P.M. Opening remarks and oral presentations, Rm. 2161
4-6 P.M. Poster presentations and refreshments, CTRB lobby

REMARKS:

Marco Pahor, MD
Director, UF Institute on Aging
Chair, Department of Aging and Geriatric Research

Roger Fillingim, PhD
UF Pain Research and Intervention Center of Excellence

Ronald Cohen, PhD
Director, Cognitive Aging and Memory Clinical Translational Research Program

SPECIAL PRESENTATIONS:

“Oxytocin and Socioemotional Aging”
Natalie Ebner, PhD
Assistant Professor, Department of Psychology
Junior Scholar, Cognitive Aging and Memory Clinical Translational Research Program and Pepper Older Americans Independence Center

“Unique Responses of the Elderly to Sepsis and Trauma”
Philip Efron, MD
Assistant Professor, Department of Surgery
Co-Director, Laboratory of Inflammation Biology and Surgical Science
Junior Scholar, Pepper Older Americans Independence Center
POSTER PRESENTATIONS

1. MARCO PAHOR, MD, Department of Aging and Geriatric Research, UF College of Medicine. The University of Florida Claude D. Pepper Older Americans Independence Center

2. STEVEN ANTON, PhD, Department of Aging and Geriatric Research, UF College of Medicine. Aspirin in Reducing Events in the Elderly (ASPREE)

3. THOMAS W. BUFORD, PhD, Department of Aging and Geriatric Research, UF College of Medicine. The Testosterone Trial (T-TRIAL)

4. LAURENCE M. SOLBERG, MD, Department of Aging and Geriatric Research, UF College of Medicine. UF Health Senior Care

5. SHINICHI SOMEYA, PhD, Department of Aging and Geriatric Research, UF College of Medicine. Biology of Aging

6. CONSTANCE UPHOLD, PhD, Department of Aging and Geriatric Research, UF College of Medicine. Geriatric Research, Education and Clinical Center (GRECC)

7. RONALD COHEN, PhD, Department of Aging and Geriatric Research, UF College of Medicine. Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP)

8. ROGER FILLINGIM, PhD, Department of Aging and Geriatric Research, UF College of Medicine; and Department of Community Dentistry and Behavioral Science, UF College of Dentistry. Pain Research and Intervention Center of Excellence (PRICE)

9. TODD MANINI, PhD, Department of Aging and Geriatric Research, UF College of Medicine. Physical Exercise to Prevent Disability: The Lifestyle Interventions and Independence for Elders (LIFE) Study
10. MI-JUNG KIM, GRADUATE STUDENT, Department of aging and geriatric research, UF college of medicine. *Mitochondrial Isocitrate Dehydrogenase and Age-Related Hearing Loss*

11. CHUL HAN, PhD, Department of aging and geriatric research, UF college of medicine. *The Roles of Glutathione Reductase in Age-Related Hearing Loss*

12. THOMAS W. BUFORD, PhD, Department of aging and geriatric research, UF college of medicine. *The Angiotensin-Converting Enzyme I/D Polymorphism and Exercise-Induced Changes in Physical Function among Caucasian Older Adults*

13. ADAM J. WOODS, PhD, Department of aging and geriatric research, UF college of medicine. *Targeting Space, Time and Causality in the Human Brain with Multimodal Neuroimaging*

14. DALLAS KHAMISS, UNDERGRADUATE STUDENT, Department of aging and geriatric research, UF college of medicine. *Effects of Rapamycin and Intermittent Feeding on Body Weight and Composition, Food Consumption and Physical Activity in Young and Old Rats*

15. AMAL A. WANIGATUNGA, GRADUATE STUDENT, Department of aging and geriatric research, UF college of medicine. *Brain Aging and Dynapenia*

16. ANGELINA G. MALMO, PhD, Department of applied physiology and kinesiology, UF college of Health and Human performance. *Effect of Resveratrol and Caloric Restriction on Mitochondrial Regulation and Apoptotic Susceptibility in Aged Rat Skeletal Muscle*

17. NICK WAWRZYNIAK, GRADUATE STUDENT, Department of applied physiology and kinesiology, UF college of Health and Human performance. *Dysregulation of Mitochondrial Quality Control Processes Contribute to Sarcopenia in a Mouse Model of Premature Aging*

18. TORRANCE J. HIGGINS, GRADUATE STUDENT, Department of applied physiology and kinesiology, UF college of Health and Human performance. *Comparison of Traditional and Task-Specific Exercise on Gait in the Pre-Clinically Disabled*

19. DAVID CLARK, ScD, Brain rehabilitation research center, U.S. Department of Veterans affairs; and Department of aging and geriatric research, UF college of medicine. *Functional Consequences and Motor Control Implications of Somatosensory Impairment in Older Adults*

20. DAVID CLARK, ScD, Brain rehabilitation research center, U.S. Department of Veterans affairs; and Department of aging and geriatric research, UF college of medicine. *Neuromuscular Activation Impairment Contributes to Emerging Mobility Deficits in Older Adults*

21. SUSAN A. LEON, PhD, Brain rehabilitation research center, U.S. Department of Veterans affairs; and Department of neurology, UF college of medicine. *Divergent Task Performance in Older Adults: Declarative Memory or Creative Potential?*

22. SUSAN A. LEON, PhD, Brain rehabilitation research center, U.S. Department of Veterans affairs; and Department of neurology, UF college of medicine. *Beyond Divergent Tasks: Novel Semantic Associations and Creativity in Aging*
23. SARAH M. SZYMKOWICZ, GRADUATE STUDENT, Department of clinical and Health psychology, UF college of liberal arts and Sciences. Preliminary Results from the Physical Activity for Mood and Memory (PAMM) Study

24. KELLY NAUGLE, PhD, Department of community Dentistry and Behavioral Science, UF college of Dentistry. Self-Reported Physical Activity Predicts Pain Inhibitory and Facilitatory Function in Older Adults

25. MEGGAN JORDAN, PhD, Department of community Dentistry and Behavioral Science, UF college of Dentistry. Careism: Using Sociological Theory to Analyze the Material and Ideological Roots of the U.S. Care System

26. YENISEL CRUZ-ALMEIDA, PhD, Department of community Dentistry and Behavioral Science, UF college of Dentistry. Psychological Profiles and Pain Characteristics of Older Adults with Knee Osteoarthritis

27. YENISEL CRUZ-ALMEIDA, PhD, Department of community Dentistry and Behavioral Science, UF college of Dentistry. Saliva as an Alternative to Plasma to Measure Biomarkers Related to Pain Mechanisms: Age Differences

28. DELORES C.S. JAMES, PhD, Department of Health education and Behavior, UF college of Health and Human performance. The Role of First-Generation College Students in Caring For Older Relatives

29. NICHOLAS MILANO, MD, Department of neurology, UF college of medicine. Improved Verbal Learning in the Semantic Variant of Primary Progressive Aphasia When Using Semantic Cues

30. TIAN LIN, PhD, Department of psychology, UF college of liberal arts and Sciences. Self vs. Other: Behavioral and Neural Evidence of the Self-Positivity Effect in Young and Older Adults

31. JOSHI GUNGEET, PhD, Department of Health education and Behavior, UF college of Health and Human performance. Attitude Differences and Preparedness to Take Care of Their Older Relatives among College Students

32. JACOB BURNS, GRADUATE STUDENT, Department of medicine, UF college of medicine. Role of Mitochondrial DNA Repair in Muscle Aging

33. ANDREW SMITH, GRADUATE STUDENT, Department of molecular genetics and microbiology, UF college of medicine. A Ribosome-Footprinting Protocol for the Study of Age-Related Genomewide Post-Transcriptional Regulation of Translation in Mammalian Tissues

34. CRISTINA BAÑUELOS, GRADUATE STUDENT, Department of neuroscience, UF college of medicine. Gabaergic Signaling Alterations Contribute to Impaired Working Memory in Aged F344 Rats
35. JENNIFER J. STAMPS, GRADUATE STUDENT, Department of Neuroscience, UF College of Medicine. A Brief Olfactory Test for Alzheimer's Disease

36. JOSEPH A. MCQUAIL, PhD, Department of Neuroscience, UF College of Medicine. Onset and Characteristics of Spatial Learning Impairment in the Aging Fisher x Brown Norway F1 Hybrid Rat

37. RICHARD HOLBERT, MD, Department of Psychiatry, UF College of Medicine. A Case Series of Transcranial Magnetic Stimulation (TMS) for Treatment-Resistant Geriatric Depression

38. YANG SHANMIN, PhD, Department of Radiation Oncology, UF College of Medicine and UF Health Cancer Center. Triptolide Inhibited Telomerase Activity and Short Telomeres in Human Tumor Cell Aging

39. RACHAEL HILTON, MEDICAL STUDENT, Department of Surgery, UF College of Medicine. Aging Depresses Protective Immunity and Prolongs Inflammation in Severe Blunt Trauma Subjects

40. JIN-HEE WANG, PhD, Department of Surgery, UF College of Medicine. Impaired Mitophagy After Ischemia/Reperfusion of Aged Mouse Livers

41. DINA C. NACIONALES, PhD, Department of Surgery, UF College of Medicine. A Failure to Resolve Inflammation Rather Than Hyper-Inflammation Characterizes the Aged Response to Severe Trauma

42. CHRISTOPHER C. LEONARDO, PhD, AND SYLVAIN DORÉ, PhD, Departments of Anesthesiology, Neurology, Psychiatry and Neuroscience, UF College of Medicine; and UF Center for Translational Research in Neurodegenerative Disease. Beneficial Stroke Outcomes Following Epicatechin Consumption in Young and Aged Mice

43. ABDULLAH SHAHIFQEH AHMAD, PhD, Department of Anesthesiology and Center for Translational Research in Neurodegenerative Disease, UF College of Medicine. Neuroprotective Effect of Prostaglandin D2, Dp1 Receptor Against Acute Brain Injuries in Young and in Aged Mice

44. CAROLYN SCOTT, UNDERGRADUATE STUDENT, Department of Biology, UF College of Liberal Arts and Sciences. Metabolic Rate of Walking in Fatigued vs. Non-Fatigued Older Adults

45. SUNIL SWAMI, GRADUATE STUDENT, Department of Aging and Geriatric Research, UF College of Medicine. Chronic Resveratrol Supplementation and Brain Oxygenation: A Pilot Study

46. LORI GENTILE, MD, Department of Surgery, UF College of Medicine. The Leukocyte Transcriptome Can Explain Immune Suppression and Effects in the Neonatal and Elderly Immune Response to Sepsis

47. KELSEY THOMAS, GRADUATE STUDENT, Department of Clinical and Health Psychology, College of Public Health and Health Professions. Age-Trajectories of Everyday Cognition in African American and Caucasian Older Adults Under Prompted and Unprompted Conditions
Event organizers:
Christy Carter, PhD
Connie Uphold, PhD
Christiaan Leeuwenburgh, PhD
Laura Pons
Brian Stanton
The University of Florida Claude D. Pepper Older Americans Independence Center

Marco Pahor, MD, Director.

We are honored to be Florida’s first Claude D. Pepper Older Americans Independence Center.

At 18.1 percent, Florida has the largest proportion of persons age 60 years or older in the nation, and this age group represents the fastest growing segment of the population in the country. Therefore it is critical that we, as the University of Florida Institute on Aging, address the health concerns of this portion of our population. In this spirit, we are proud to have received funding from the National Institute on Aging to establish the Claude D. Pepper Older Americans Independence Center (OAIC).

The mission of the UF-OAIC is to assess the risk factors of physical disability in older adults, develop and test effective prevention therapies, and train new investigators in research on aging and disability, while developing their leadership qualities.

Our center’s research theme of “sarcopenia and prevention of disability” is pursued using an interdisciplinary approach that traverses the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral sciences and epidemiology.

This research theme addresses the general goal of the OAIC program, namely to increase scientific knowledge that leads to better ways to maintain or restore independence of older persons.

To address our overall objectives, the OAIC includes several integrated Cores, which support investigators, Junior Scholars, infrastructure, and services: the Leadership and Administrative Core, the Research Career Development Core, the Pilot/Exploratory Studies Core, the Clinical Translational Research Core, the Metabolism and Biomarkers Core, the Biostatistics and Data Management Core, and the Recruitment, Adherence and Retention Core.
Aspirin in Reducing Events in the Elderly (ASPREE)

Stephen D. Anton, PhD, Department of Aging and Geriatric Research, UF College of Medicine.

Aspirin may prolong life by preventing disease. Low dose aspirin reduces the risk of heart attack, stroke and vascular events in middle aged adults and may help prevent cognitive decline and certain cancers. However, side effects of aspirin, such as bleeding, are more common in older persons and may offset its benefits. ASPREE is a double-blind, randomized, placebo-controlled primary prevention trial designed to assess whether daily active treatment of 100 mg enteric-coated aspirin will extend the duration of disability-free life in healthy participants aged 70 years and above except for Hispanic and African American minority groups in the USA where the minimum age of entry is 65 years. The study will examine whether the potential benefits of low dose aspirin (particularly the prevention of heart disease, stroke, certain cancers and dementia) outweigh the risks (particularly severe gastrointestinal bleeding and hemorrhagic stroke) in this age group. Participants are eligible for the trial if they do not have a current clinical indication for (i.e. overt cardiovascular disease) or contraindication to (i.e. allergy or increased risk of bleeding) aspirin, do not have dementia, disability, low hemoglobin levels, or have a condition that is likely to be fatal during the 5 years of the trial and are capable of providing informed consent. Nineteen thousand participants will be required to provide 90% power of a true relative risk benefit of 0.90 for the primary endpoint (a composite of all-cause mortality, incident dementia and persistent physical disability) in an intention-to-treat analysis with an average follow-up of 5 years. Thus, this trial will provide a definite answer regarding the benefit-to-risk ratio of long-term aspirin use in older adults. The trial has received financial support from the National Institute on Aging (part of the National Institutes of Health), the National Health and Medical Research Council of Australia, the National Heart Foundation of Australia and the Victorian Cancer Agency. Bayer Schering Pharma provides in kind support through the provision of low dose aspirin and matching placebo. The study will be carried out in community settings in the USA and Australia. In the USA, 6,500 participants will be recruited through clinical trials networks in regional hub settings. In Australia, recruitment of 12,500 participants will take place through general practices with the participant’s usual treating General Practitioner (GP) as co-investigator.
**THE TESTOSTERONE TRIAL: A PHASE 3 RANDOMIZED CONTROLLED TRIAL FOR OLDER MEN**

Stephen D. Anton, Michael Marsiske, Susan Nayfield, Todd M. Manini, Bhanuprasad Sandesara, Thomas W. Buford, & Marco Pahor

Department of Aging and Geriatric Research

**Purpose:** As men age their blood testosterone levels fall, and also they find it more difficult to walk, have less energy, have less interest in sex, have greater difficulty remembering, and tend to be anemic, as well as greater risk of cardiovascular disease. It is possible that low blood testosterone is a cause of these problems. The purpose of The Testosterone Trial is to determine if testosterone treatment of men who are 65 years and older – and who have a low blood testosterone and one or more of these problems – will improve them.

**Brief Description:** The Testosterone Trial is a multicenter study of six coordinated trials of the effects of testosterone in elderly men with low testosterone on physical function, vitality, sexual function, cognitive function, anemia, and cardiovascular risk. Eight hundred men ≥65 years whose serum testosterone is <250 ng/dL are being randomized to receive testosterone or placebo double blindly for one year. The primary end points for each trial are distance walked in 6 minutes, fatigue-vitality, sexual activity, delayed verbal memory, hemoglobin, and coronary artery plaque burden. There are also several secondary end points for each trial.

**Eligibility:** To qualify for The Testosterone Trial, a man must be 65 years or older and have a serum testosterone concentration less than 250 ng/dL at 8AM on two occasions. He must also have symptoms and measured functional impairments in walking, sexual interest, or vitality. Men must also be at relatively low risk for prostate cancer and not have severe lower urinary tract symptoms.

**Treatment:** Men who qualify and agree to participate will be assigned randomly to receive either a testosterone gel or a placebo gel for one year. The dose of testosterone gel will be adjusted to keep the serum testosterone concentration within the normal range for young men.
DIVISION OF BIOLOGY OF AGING
Someya, Shinichi (Department of Aging and Geriatric and Research, University of Florida); Carter, Christy (Department of Aging and Geriatric and Research, University of Florida); Joseph, Anna-Maria (Department of Aging and Geriatric and Research, University of Florida); Leeuwenburgh, Christiaan (Whitney Lab, University of Florida)

Abstract:
The Division of Biology of Aging vision focuses on research to enhance and extend the human health span through a better understanding of the biological mechanisms and the functional consequences that underlie the aging process. This includes the full spectrum of research from applying discoveries made in the laboratory, developing trials and studies for humans, and enhancing the adoption of best treatment practices into the medical community.

The division’s goals are to identify and investigate novel opportunities to better understand the mechanisms of aging, and to provide research service, seminars and education to investigators within UF and the national aging research community.

The objectives of the division’s research are to elucidate the biochemical, genetic, and physiological mechanisms of aging that result in age-related functional (both physical and cognitive) decline in humans and animal models. This includes investigations of the gradual or programmed alterations of structure and function that characterize normal aging, and investigations of the adverse changes that are risk factors for or accompany age-related disease states.

The division’s current broad research areas include:

1. Animal Models (Function and Behavior).
2. Musculoskeletal Biology (Function, Physiology and Biochemistry).
3. Cardiovascular Biology (Function, Physiology and Biochemistry).
4. Sensory Biology (Function, Physiology and Biochemistry).

The ultimate goal of our research program is to better understand why and how we age at the molecular, cellular, and tissue levels.
Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP)

Program Supported by the McKnight Brain Research Foundation.

Program Director: Ron A. Cohen, Ph.D., ABPP, ABCN

Approximately one in seven adults over the age of 65 experience moderate to severe cognitive impairments, including problem with memory. These impairments adversely impact the ability of the elderly to remain functionally independent, and also interfere with health status and quality of life. People are increasingly reaching very advanced age, and there is evidence that the prevalence of cognitive and memory dysfunction will approach fifty percent among centenarians, providing a strong rationale for an intensification of clinical and translational neuroscience directed at age-associated cognitive decline. Research is needed to identify biomarkers that can identify people at risk for functional decline and early signals that changes in the brain are occurring prior to onset of overt symptoms. There is also a major need for research aimed at developing new interventions to prevent and remediate age-associated cognitive problems before disabling functional decline occurs. The Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP) addresses this critical need.
Pain Research and Intervention Center of Excellence (PRICE)

Roger Fillingim, PhD, Department of Aging and Geriatric research, UF College of Medicine; and Department of Community Dentistry and Behavioral Science, UF College of Dentistry.

Chronic pain represents the most prevalent and costliest public health condition affecting the United States; therefore, an improved understanding of chronic pain, leading to more effective pain treatments, is urgently needed. The University of Florida Pain Research and Intervention Center of Excellence (PRICE) endeavors to reduce pain-related suffering throughout Florida and the nation through excellence in pain research, treatment and education, which ultimately will be achieved by integrating all three missions under one interdisciplinary Center of Excellence. PRICE is a multi-college Center of Excellence that serves as the professional home for UF’s nationally recognized cadre of more than 40 multidisciplinary UF scientists, clinicians and trainees dedicated to improved understanding and treatment of pain. PRICE is affiliated with the UF Clinical and Translational Science Institute (CTSI) and receives strong support from the UF Institute on Aging and the UFHealth Cancer Center. PRICE provides investigators with resources and services in order to facilitate clinical and translational pain research at UF. A major PRICE resource is the Pain Clinical Research Unit (PainCRU), a patient-oriented research venue that provides facilities and personnel to support clinical and translational pain research at UF. The PainCRU occupies more than 2,000 square feet of laboratory space across three locations at the UF Health Sciences Center, including the new Clinical and Translational Research Building, with locations in both the Clinical Research Center and Institute on Aging (IOA). The IOA collaboration is particularly valuable, because PRICE investigators are national leaders in pain and aging research. Indeed, PRICE researchers are conducting novel and important studies to elucidate age-related changes in the functioning of the pain system, which represents a primary focus of research for PRICE. In addition, PRICE-affiliated investigators are pursuing several other pain research themes, including: the influence of gender, race and ethnicity on pain responses and decisions about pain treatment; determining risk factors for development of chronic pain disorders; uncovering central nervous system factors influencing placebo analgesia; exploring mechanisms of musculoskeletal pain; explicating interactions between pain and sleep; and identifying contributors to pain following cancer treatment. By providing infrastructure and resources to facilitate pain research and by enabling increased collaboration and interaction among UF pain scientists, PRICE intends to transform the UF pain research enterprise, leading to novel discoveries that will ultimately and improve pain treatment in Florida and throughout the country.
Physical Exercise to Prevent Disability: The Lifestyle Interventions and Independence for Elders (LIFE) Study

Todd Manini, Thomas Buford, Steve Anton, Bhanuprasad Sandesara, Michael Perri, Christiaan Leeuwenburgh and Marco Pahor

Key words: Exercise, disability, aging, clinical trial, physical activity

As life expectancy in the US continues to rise, maintaining independence among older Americans has emerged as a major clinical and public health concern. Older people who lose mobility are less likely to remain in the community, have higher rates of morbidity, mortality and hospitalizations, and experience poorer quality of life. Several studies have shown that regular physical activity improves physical performance, but definitive evidence that it prevents mobility disability is lacking. The Lifestyle Interventions and Independence for Elders (LIFE) Study, recently funded by the National Institute on Aging, is a Phase 3, multicenter randomized controlled clinical trial (RCT) comparing a moderate-intensity Physical Activity (PA) program to a Successful Aging (SA) health education program in sedentary persons ages 70-90 years who are at risk of disability. 1635 participants are being enrolled at eight field centers and followed for an average of 2.7 years. Individuals randomized to PA perform moderate intensity walking and resistance exercise 3-6 days per week. The SA group undergo lifestyle education sessions and upper extremity stretching exercises 2-4 times per month. The primary outcome is development of major mobility disability defined as inability to walk 400 m. Secondary and tertiary outcomes comprise cognitive function; serious fall injuries; persistent mobility disability; the combined outcome of major disability disability or death; disability in activities of daily living; cardiovascular and cardiopulmonary events; mild-cognitive impairment or dementia; health-related quality of life (depressive symptoms, sleep quality, stress, satisfaction with life); and cost-effectiveness of the intervention. As compared to a lifestyle education group, this RCT will determine whether physical activity is effective and practical for preventing major mobility disability in sedentary older persons. The results will have crucial implications for public health in a rapidly aging society and will fill an important gap in evidence-based geriatric practice.
MITOCHONDRIAL ISOCITRATE DEHYDROGENASE AND AGE-RELATED HEARING LOSS

Kim, Mi-Jung (Department of Aging and Geriatric and Research, University of Florida); Walker, Logan (Department of Aging and Geriatric and Research, University of Florida); Han, Chul (Department of Aging and Geriatric and Research, University of Florida); Linser, Paul (Whitney Lab, University of Florida); Someya, Shinichi (Department of Aging and Geriatric and Research, University of Florida)

Abstract:
Mitochondrial isocitrate dehydrogenase 2 (IDH2) plays a critical role in the TCA (tricarboxylic acid) Cycle in the mitochondrial matrix through converting isocitrate to α-ketoglutarate and reducing NADP⁺ to NADPH. IDH2 also plays a central role in regeneration of mitochondrial glutathione and thioredoxin by supplying NADPH to mitochondrial NADPH-dependent glutathione reductase and thioredoxin reductase. Evidence indicates that decreased expression of Idh2 results in elevated levels of hydrogen peroxide and oxidative damage, while overexpression of Idh2 protects the cells from ROS-induced cell death in mouse fibroblasts. Our preliminary evidence indicates that CR (calorie restriction) delays the onset of AHL (age-related hearing loss), reduces oxidative DNA damage and cochlear cell loss, and increases the activities of glutathione reductase and thioredoxin reductase, NADPH levels, and IDH2 activity in the mitochondria of mouse cochlea. Therefore, our central hypothesis is that mitochondrial Idh2 plays an essential role in the CR-mediated prevention of AHL, the most common sensory disorder. We are currently investigating the roles of Idh2 in slowing the progression of AHL, protecting the cochlear cells from oxidative stress, and enhancing mitochondrial function and antioxidant defenses, and regulating the redox status of mitochondria in the cochlea during aging and under CR conditions using cultured Idh2 knockdown mouse inner ear cells and Idh2 KO mice. These are fundamental biological questions that apply to all sensory cells, neurons, and common age-related sensory disorders. Moreover, the results of this project will provide an enhanced understanding of the fundamental molecular mechanisms underlying aging of the sensory systems.
THE ROLES OF GLUTATHIONE REDUCTASE IN AGE-RELATED HEARING LOSS

Han, Chul (Department of Aging and Geriatric Research/University of Florida); Kim, Mi-Jung (Department of Aging and Geriatric Research/University of Florida); Walker, Logan (Department of Aging and Geriatric Research/University of Florida); Rielo Diego (Department of Aging and Geriatric Research/University of Florida), Linser, Paul (Whitney Lab/University of Florida); Someya, Shinichi (Department of Aging and Geriatric Research/University of Florida)

Abstract:
Glutathione acts as the major small molecule antioxidant in cells and is found mostly in the reduced form (GSH) in healthy mitochondria. During aging, oxidized glutathione (GSSG) accumulates, and hence an altered ratio of mitochondrial GSH:GSSG is thought to be a marker of both oxidative stress and aging. Glutathione reductase (GSR) plays a critical role in preventing accumulation of GSSG and maintaining the appropriate redox environment in the mitochondria through regeneration of GSH, thereby enhancing the glutathione antioxidant defense system. Our preliminary evidence indicates that CR (calorie restriction) delays the onset of AHL (age-related hearing loss), reduces oxidative DNA damage and cochlear cell loss, and increases the activity of glutathione reductase and GSH/GSSG ratio in the mitochondria of mouse cochlea. Therefore, our central hypothesis is that Gsr plays an essential role in protecting the inner ear from oxidative stress and slowing the development of AHL during aging or under CR conditions in mammals. Using cultured GSR knockdown mouse inner ear cells and Gsr KO mice, we found that: 1) Gsr is present in the hair cells and spiral ganglion neurons in the cochlea. 2) Gsr does not play a crucial role in development of mouse inner ear. 3) knockdown of GSR increases susceptibility to oxidative stress-induced cell death in mouse inner ear cells. Currently, we are investigating the roles of Gsr in slowing the progression of AHL and enhancing mitochondrial function and antioxidant defenses during aging and under CR conditions. Knowledge of these molecular mechanisms has enormous potential for improving health outcomes through the discovery/development of novel therapeutics for human AHL and other age-related sensory disorders.
Maintaining the physical independence of older adults is an important public health challenge. To date, physical exercise is the only intervention consistently shown to attenuate age-related declines in physical function. However, extreme variability exists in the responsiveness of older adults to training. Numerous studies have demonstrated the influence of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism on various physiologic adaptations to exercise. However, evidence is inconclusive regarding the influence of this variant on changes in physical function among seniors following training.

PURPOSE: To evaluate the association of I/D genotypes with changes in physical function among pre-disabled older adults (aged ≥ 70 years) following engagement in a 12-month exercise training intervention.

METHODS: Data are from Caucasian participants (n= 282) in the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study. LIFE-P was a multi-site, randomized clinical trial which compared the effects of multimodal exercise training to those of a successful aging health education program. Measures of physical function included self-paced gait speed and performance on the Short Physical Performance Battery (SPPB). Genotypes were determined using polymerase chain reaction and agarose gel electrophoresis. Hardy-Weinberg equilibrium was checked using the chi-square test. The genotype*treatment interaction for each outcome was evaluated using linear regression. Covariates included clinic site, body mass index, age, gender, baseline score, co-morbidity, and use of angiotensin receptor blockers or ACE inhibitors.

RESULTS: Genotype frequencies [II (19.5%), ID (41.8%), DD (38.7%)] were in Hardy-Weinberg equilibrium (p > 0.05). The genotype*treatment interaction was significant for gait speed (p < 0.001) while a trend toward significance was observed for the SPPB test (p = 0.085). Exercise improved gait speed 0.06 ± 0.01 m/sec and SPPB score 0.75 ± 0.17 points among ID/DD carriers, but performance was not improved among II carriers.

CONCLUSION: ACE I/D genotype appears to play an important role in modulating senior’s functional responses to exercise training.

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TARGETING SPACE, TIME, AND CAUSALITY IN THE HUMAN BRAIN WITH MULTIMODAL NEUROIMAGING

Woods, Adam J. (Aging and Geriatric Research, Institute on Aging, Center for Cognitive Aging & Memory, University of Florida); Chatterjee, Anjan (Neurology, Center for Cognitive Neuroscience, University of Pennsylvania)

The capacity to infer causality is a central human ability that is constructed from elemental spatial and temporal information in events. This ability allows us to interpret events in our environment, predict future outcomes, and plan goal-directed actions. Recent data suggests that older adults are less sensitive to the relationship between time and causality than younger adults – a factor that may have profound consequences for decision-making. While this lack of sensitivity cannot be explained by decline in temporal perception, its cause(s) remain unknown. The present two experiments used a novel multimodal neuroimaging paradigm to identify the neural correlates of causality and explore feasibility for intervention studies. As the neural correlates of causality remain poorly understood, we first used functional magnetic resonance imaging (fMRI) to generate hypotheses for candidate brain regions related to spatial, temporal, and decision-making contributions to causal inferences (Experiment 1). Participants in both experiments judged causality in billiard-ball style launching events; a blue ball approaches and contacts a red ball. Space and time were parametrically manipulated by depicting different violations of spatial linearity and temporal contiguity in events. Results demonstrated three distinct patterns of activation in association with spatial (bilateral fronto-parietal networks), temporal (right hippocampal and cerebellum), and decision-making (inferior frontal gyrus and insula) components of causal inferences (Family-Wise Error Cluster Thresholds p<.05). In Experiment 2, we used transcranial direct current stimulation (tDCS), a form of non-invasive brain stimulation, to test hypotheses for the specific roles of the frontal and parietal patterns of activation from fMRI. Parietal tDCS stimulation only decreased participants’ acceptance of spatial violations when inferring causality, while frontal stimulation made participants less likely to accept violations of both space and time (Generalized Linear Model: Session x Location: $X^2=6.4$, p=.04). Converging results from fMRI and tDCS indicate that the parietal cortex contributes to causality because of its specific role in processing spatial relations and the frontal cortices contribute more generally, consistent with their role in decision-making. These data provide insight important for future studies investigating aging-related changes in causal inference. This multimodal paradigm may prove useful for future intervention studies targeting aging, psychiatric, and neurological populations.
EFFECTS OF RAPAMYCIN AND INTERMITTENT FEEDING ON BODY WEIGHT AND COMPOSITION, FOOD CONSUMPTION, AND PHYSICAL ACTIVITY IN YOUNG AND OLD RATS

Rapamycin, a chemical initially of interest for its antifungal properties, has since grown popularity not only as an immunosuppressant for organ transplantation but also as drug for cancer treatment. Rapamycin is an inhibitor of the mammalian target of rapamycin (mTOR) pathway, which regulates cellular activities such as cell growth and survival, nutrient sensing, protein synthesis, and autophagy. Although rapamycin has also been shown to increase mammalian lifespan, less is known concerning its role as a modulator of mammalian healthspan. For that reason, the primary aim of this study was to examine rapamycin’s role in the alteration of food consumption, body composition, and physical activity in a rat model.

Male Fisher 344 x Brown Norway (F344BN) rats, 6 and 25 months, were assessed at baseline for body weight, food intake, body composition, grip strength, and locomotor activity prior to being randomized into three treatment groups: rapamycin (n=20), intermittent feeding (IF) (n=20), and control (n=20). IP injections were given to all treatment groups three times per week, and treatment lasted five weeks. Rapamycin-treated animals received 1 mg/kg rapamycin, while 1 mg/kg vehicle was administered to IF and control animals. Animals were sacrificed by rapid decapitation, and trunk blood was processed for determination of serum leptin.

Rapamycin and IF treatment reduced food consumption and body weight in both age groups. Regarding body composition, rapamycin treatment yielded increases in lean/muscle mass and decreases in fat mass, providing a lean/fat mass ratio similar to young control rats. IF treatment failed to alter fat mass and resulted in lower levels of lean mass. Rapamycin and IF treatment yielded significant decreases in hypothalamic levels of total AMPK and pAMPK only in old animals. In the behavioral tasks, rapamycin treatment yielded high levels of activity (similar to the baseline levels) only in old animals, while IF treatment yielded increased levels of “anxiety” for both ages. Grip strength was not significantly altered by either treatment. Thus, a general pattern of results suggests that IF tends to alter behavior and physiology in the same manner regardless of age, while rapamycin had more selective effects on old animals.
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TITLE:
BRAIN AGING AND DYNAPEFIGEN

ABSTRACT:
Factors that underlie age-related reductions in muscle strength (Dynapenia) are not completely understood. Brain abnormalities that are common in older adults might partially explain the decline in muscle strength. The objective of this study was to evaluate the association between muscle strength and structural (macro and micro) brain abnormalities in older adults. Maximal knee extension strength and magnetic resonance imaging derived brain morphometry and integrity was collected in 273 cognitively intact older adults (82.7 ± 2.7 years). White matter hyperintensity volume was associated with -7.4 [Standard error (SE): 3.4] N·m lower muscle strength. Higher gray matter volume was associated with 6.9 [SE: 3.6] N·m greater muscle strength. Increased mean diffusivity of gray matter – a measure of tract integrity – was associated with -7.7 [SE: 3.8] N·m lower muscle strength. Higher white matter magnetization transfer ratio – another measure of tract integrity – was also linked to higher levels of muscle strength. These results indicate both white matter and gray matter macro- and micro-structural abnormalities are associated with muscle strength in older adults.
EFFECT OF RESVERATROL AND CALORIC RESTRICTION ON MITOCHONDRIAL REGULATION AND APOPTOTIC SUSCEPTIBILITY IN AGED RAT SKELETAL MUSCLE

Sarcopenia is an age-related loss in muscle mass partially attributable to mitochondrial-mediated apoptosis. Caloric restriction (CR) and resveratrol (RSV) treatment in rodents induces beneficial mitochondrial alterations which may serve to suppress sarcopenia. Doxorubicin (DOX) is a chemotherapeutic agent that induces cell death via mitochondria. We investigated whether RSV (50mg/kg/day; 6 weeks) and/or CR (20% reduced AL; 6 weeks) could 1) induce mitochondrial biogenesis, 2) attenuate apoptotic susceptibility and, 3) reduce DOX-induced toxicity, in aged rodent muscle. Aged F344xBN rats (26 mo) were split into 8 groups (n=4): ad libitum (AL), CR, RSV, RSV+CR and injected with DOX (20 mg/kg; IP) or saline prior (24h) to sacrifice. Mitochondrial content/regulation (cyto c, COX activity, PGC-1α, SIRT3) and apoptotic susceptibility (Bax:Bcl-2) were assessed in hindlimb muscle. Surprisingly, mitochondrial indices were unaffected by CR, RSV or RSV+CR, and DOX did not affect any group. CR+RSV reduced (50%) the Bax:Bcl-2 in AL while CR, RSV and RSV+CR tended to suppress this DOX-induction. Our data indicated aged muscle, and DOX-treatment, increases apoptotic susceptibility and RSV+CR treatment provides modest protection without altering mitochondrial content/regulation.
DYSREGULATION OF MITOCHONDRIAL QUALITY CONTROL PROCESSES CONTRIBUTE TO SARCOPENIA IN A MOUSE MODEL OF PREMATURE AGING

Mitochondrial DNA (mtDNA) mutations lead to decrements in mitochondrial function and accelerated mtDNA mutational rates are linked to skeletal muscle loss (sarcopenia). We investigated the effect of mtDNA mutations on mitochondrial quality control processes in skeletal muscle from animals (young; 3-6 months and older; 8-15 months) expressing a proofreading-deficient version of mtDNA polymerase gamma (PolG). PolG animals exhibit elevated mtDNA mutation rates, mitochondrial dysfunction, and a premature aging phenotype, including sarcopenia. The mitochondrial biogenesis regulator peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) and its target proteins, nuclear respiratory factor 1 (NRF-1) and mitochondrial transcription factor A (Tfam) in PolG animals were increased compared to wild-type (WT) (P<0.05). Older PolG animals displayed higher mitochondrial fission protein 1 (Fis1) and greater autophagy (P<0.05). In contrast, muscle from normally-aged animals exhibited a different expression profile compared to PolG animals. Older WT animals had higher fusion (higher Mfn2 and lower Fis1) and lower autophagy-related machinery (Beclin-1 and p62) compared to young WT suggesting autophagy is impaired in aging muscle. In conclusion, muscle from mtDNA mutator mice display higher mitochondrial fission and autophagy levels that likely contribute to the premature sarcopenic phenotype.
COMPARISON OF TRADITIONAL AND TASK-SPECIFIC EXERCISE ON GAIT IN THE PRE-CLINICALLY DISABLED

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Objective. Compare walking performance following a task-specific exercise (TSE) intervention and a recommended program by the National Institute on Aging (NIA) that includes walking, balance, and resistance exercise in pre-clinically disabled older adults.

Methods. Sixty-nine pre-clinically disabled older adults (69.9 ± 8.35 years) were tested. They reported no difficulty performing typical daily tasks, but modified the method or frequency with which daily tasks were executed. Interventions were conducted 2 times per week for 12 weeks. TSE training included rising from a chair and the floor, climbing stairs, and gait challenges (e.g., navigating obstacles). Spatiotemporal gait parameters were recorded with and without shoes under single and dual task (counting backwards by three’s starting from 100, 50, and 25) conditions using an instrumented walkway system (GAITRite® mat).

Results. TSE training increased gait velocity and cadence under single (mean change, 6.65 cm/sec [2.00], p = 0.03 and 3.39 steps/min [0.96], p = 0.02, respectively) and dual (mean change, 5.32 cm/sec [2.30], p = .023 and 4.06 steps/min [1.15], p = .01, respectively) task conditions, compared to the NIA program. TSE training increased base of support (mean change, 0.57 cm [0.23], p = 0.03) under dual task conditions, compared to the NIA intervention (mean change, -0.17 cm [0.24]). No significant changes in step variability were observed. Similar results were found with shoes-off conditions.

Discussion. TSE training improves gait velocity and cadence significantly more than the current NIA exercise recommendation aimed to prevent physical disability in at risk older adults.
FUNCTIONAL CONSEQUENCES AND MOTOR CONTROL IMPLICATIONS OF SOMATOSENSORY IMPAIRMENT IN OLDER ADULTS

Age-related impairment of peripheral somatosensation may disrupt the automatic neural control mechanisms of balance and gait, leading to mobility deficits. Brain imaging studies have proposed that a compensatory strategy involving heightened cerebral control of task performance may counteract the detrimental effects of peripheral impairments. If so, one would expect that mild somatosensory impairment would not substantially diminish mobility function. However, there is currently a lack of behavioral evidence to support this assertion. The purpose of this study is therefore to further investigate the relationship between somatosensation and mobility function. Consistent with the proposed existence of an effective compensatory neural control strategy, we hypothesize a non-linear relationship such that deficits in mobility function will be found with moderate but not mild somatosensory impairment. Cutaneous tactile perception was assessed at four sites on the plantar surface of each foot using a Semmes–Weinstein 5.07 (10g) monofilament. Vibratory perception was tested on the dorsal surface of each great toe using a 128-Hz tuning fork. Mobility was assessed with the Berg Balance Scale, usual walking speed and maximal walking speed. Polynomial regression analyses were performed to examine whether the relationship between somatosensation and mobility were best described by a linear or non-linear (quadratic, exponential and logistic) function. Sixty-one older adults participated (mean age 74.5±6.6 years). Tactile perception at each plantar site was significantly association with Berg Balance score (p≤0.002). For the site located at the head of the first metatarsal, tactile perception was also associated with usual and maximal walking speed (p≤0.005). Vibratory perception was significantly associated with Berg Balance score (p<0.0001) and usual walking speed (p<.01). These associations were found to be linear, as non-linear functions did not account for additional variability. We also compared mobility function between subgroups of older adults with no detectable impairment versus those with mild impairment. These comparisons revealed clinically meaningful deficits in mobility function for the subgroups with mild impairment. The findings of this study indicate that mild impairment of somatosensation contributes to substantial mobility deficits in older adults. Accordingly, this study does not support the assertion that a compensatory neural control strategy effectively counteracts impaired somatosensation.
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NEUROMUSCULAR ACTIVATION IMPAIRMENT CONTRIBUTES TO EMERGING MOBILITY DEFICITS IN OLDER ADULTS

Walking deficits in older adults threaten functional independence and reduce quality of life. Walking deficits develop gradually, such that an individual may appear to have normal function for a number of years despite a progression of underlying impairments. Little is known about what key impairments contribute to the onset of walking deficits. Identifying these impairments will be critical for facilitating early detection and early intervention to prevent the occurrence of overt walking deficits. The objective of this study is to acquire preliminary data to assess whether impaired neuromuscular activation of the plantarflexor muscle group may contribute to the onset of walking deficits in healthy, high functioning older adults. Participants were recruited to a “FASTER” group (n=12) and a “SLOWER” group (n=8). Maximal walking speed was the criterion used to differentiate between groups. All participants had a preferred 10m walking speed within the normal range of 1.0-1.4 m/s. Individuals in the FASTER group were also required to have a maximal 10m walking speed at least 0.7 m/s above preferred speed. Individuals in the SLOWER group were required to have a maximal 10m walking speed less than 0.6 m/s above preferred speed. Leg muscle cross sectional area (CSA) was assessed with MRI. During a rapid bilateral heel-rise task, neuromuscular activation and force production were quantified as Rate of EMG Rise and Rate of force production, respectively. FASTER and SLOWER did not differ for age, gender, body weight, body mass index, Berg Balance Score or Mini-Mental State Exam score. Muscle CSA was not larger in FASTER than SLOWER for plantarflexors, quadriceps or hamstrings. Neuromuscular performance was worse in SLOWER, including lower Rate of EMG Rise (p=0.01) and lower Rate of Force Production (p=0.002). Across all participants, Rate of EMG Rise was found to be positively associated with 400m walking speed and maximal walking speed. The findings of this study suggest that impaired neuromuscular activation of the plantarflexor muscle group is an important determinant of walking speed in older adults who are still well-functioning. Accordingly, impaired neuromuscular activation may be a factor contributing to the initial onset and progression of walking deficits in older adults.
DIVERGENT TASK PERFORMANCE IN OLDER ADULTS: DECLARATIVE MEMORY OR CREATIVE POTENTIAL?

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Introduction: Divergent thinking is the ability to produce a range of responses or solutions and is an element of creative processing. Divergent thinking requires disengagement, the ability to associate between words or ideas, and the production of responses. Lesion and imaging studies have shown frontal-lobe involvement for these activities, and frontal lobe function is highly dependent on white matter pathways. Normal aging often results in deficits in functions controlled by the frontal lobes as well as decrements in white matter connectivity. Objectives: The objectives of this study were to compare non time-constrained tasks of verbal divergent processing in young adults (YAs) and older adults (OAs) and correlate performance with tasks of language ability, working memory, and disengagement/inhibition. Methods: The participants were 30 healthy YAs aged 18-30 and 30 healthy OAs aged 65-80. Participants were all right handed, native speakers of English with at least 12 years of education. Lexical-semantic knowledge was assessed using two vocabulary tests, a standardized battery and a 40 item measure of descriptive auditory naming. Working memory was assessed using an operation span task and disengagement/inhibition was assessed using a STROOP paradigm. Two verbal tasks of divergent thinking were used in this study. The first was the Alternate Uses test in which participants are asked to list alternate or unusual uses for common objects. This test was designed to assess flexibility, originality, and fluency of divergent thinking. The second task was an Associative Fluency task, in which participants were told to list alternate or unusual uses for common objects. This test was designed to assess flexibility, originality, and fluency of divergent thinking. Results: Contrary to our a priori hypothesis, OAs produced statistically significantly more unique responses on both divergent tasks than YAs, although total fluency was not significantly different. Correlational analyses examining the groups together and separately revealed a number of differences suggesting that the groups were utilizing different underlying cognitive abilities to complete these tasks. We propose that the primary factor resulting in higher uniqueness scores on these common divergent thinking tasks for the OAs was a greater wealth of experience as well as longer exposure to language use.
Introduction: While there is reported neuronal atrophy of cortical regions in healthy aging primarily in frontal regions, the most substantial loss is seen in white matter tracts. Due to changes in structure and function of these tracts that enable inter and intra-hemispheric connectivity, it is possible that accessing and activating diffuse semantic networks may be altered in older adults. Older adults have been shown to have a greater number of semantic representations as evidenced by higher performance on vocabulary tests, but deficits in accessing representations have also been reported. **Objective:** The objective was to compare performance in healthy young adults (YAs) and older adults (OAs) on a storytelling task using three semantically unrelated words; this requires a synthesis of novel semantic associations, and has been shown in fMRI studies to activate regions of the temporal, parietal and frontal lobes bilaterally. **Methods:** The participants were 30 healthy YAs aged 18-30 and 30 healthy OAs aged 65-80. The participants were given tests of language ability, working memory, disengagement/inhibition, and two verbal divergent processing tasks. Participants were then asked to produce four stories incorporating lists of semantically unrelated words. Stories were recorded, transcribed, and rated by independent trained judges blinded to age group. Stories were rated on 5 categories: novelty/originality, cohesiveness, organization, appropriateness and overall score. **Results:** There was a highly significant group effect in favor of YAs (p < .001) with YA's stories rated as being significantly more creative and appropriate. However, the OA participants had been able to produce statistically significantly more unique responses on two verbal divergent processing tasks, results which would seem at odds. We propose that this difference is due to the enforced novelty of the storytelling task used in this study. While OAs were able to produce more unique responses in tasks where previous knowledge could be utilized, they demonstrated more difficulty creating novel semantic associations despite their greater lexical semantic stores. The deficit in OAs ability to creatively form novel connections between existing semantic representations may be due to white matter decrement as well as deficits in functions controlled by the frontal lobes.
PRELIMINARY RESULTS FROM THE PHYSICAL ACTIVITY FOR MOOD AND MEMORY (PAMM) STUDY

Previous work has suggested that a history of depression is associated with persistent structural and functional changes in frontolimbic regions, particularly in older adults. Identifying interventions that not only improve mood but also address underlying brain changes is crucial. Research suggests that aerobic exercise (AE) helps relieve symptoms of depression and also leads to neurogenesis and increased blood flow to frontal and temporal regions. The goal of this pilot study was to determine whether older adults with a history of depression show functional changes after an AE intervention. Functional magnetic resonance imaging (fMRI) was used to examine neural correlates of memory encoding in 9 older adults (mean age 64.44 ± 6.93 years) with (n = 6) or without (n = 3) a history of depression before and after an AE intervention. The AE intervention involved walking on an indoor track for one hour, three times a week for 24 sessions over 8-12 weeks. Participants underwent neuroimaging no more than 2 weeks prior to starting the exercise intervention and were scanned again within 1 week of completing the intervention. fMRI data were acquired while participants completed a verbal memory task that involved memorizing items on a categorizable shopping list and analyzed using random-effects whole-brain voxel-wise general linear models. Compared to controls, participants with a history of depression showed significantly increased activation following AE within the prefrontal cortex and middle temporal gyrus (3D spatial contiguity threshold of 20 voxels; p ≤ .01). While preliminary, these results suggest that encoding-related brain function is affected by an exercise intervention in older adults who have a history of depression. Future work will seek to replicate these results in a larger sample to determine if AE is an effective intervention for persistent cognitive and brain changes in older adults with a history of depression and to determine whether changes in depressive symptoms after AE are linked to changes in functional activation. These results highlight the role that AE may have as a non-pharmacological intervention for geriatric depression.
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SELF-REPORTED PHYSICAL ACTIVITY PREDICTS PAIN INHIBITORY AND FACILITATORY FUNCTION IN OLDER ADULTS

Data from observational studies, randomized control trials, and laboratory studies suggest a relationship between levels of physical activity and chronic pain. The experience of pain is a complex phenomenon under the control of endogenous systems that both facilitate and inhibit pain. Dysfunction of endogenous facilitatory and inhibitory systems has been implicated in multiple chronic pain conditions and older adults. However, no studies have investigated the relationship between levels of physical activity and descending pain modulatory function. The purpose of this study was to determine whether self-reported levels of physical activity in healthy older adults was associated with 1) pain facilitatory function as tested by temporal summation of pain (TS), and 2) pain inhibitory function as tested by conditioned pain modulation (CPM). Twenty-two healthy adults (age range 55-76) completed the International Physical Activity Questionnaire (IPAQ) and the psychophysical tests of temporal summation of heat pain and conditioned pain modulation. The IPAQ measured levels of walking, moderate, vigorous and total physical activity over the past seven days. Subjects were divided into high and low physical activity (PA) groups based upon a median split of total physical activity score. Measures on the pain tests were compared between groups, while controlling for sex. Additionally, partial correlations were conducted to determine the relationship between each pain test and self-reported levels of physical activity, while controlling for sex. The results revealed that the high PA group exhibited significantly more pain inhibition on the CPM test and less pain facilitation on the TS test compared to the low PA group. Self-reported total physical activity was significantly associated with TS ($r=-.696$) and CPM ($r=.515$). Individuals who self-reported more total physical activity exhibited reduced temporal summation of pain and greater CPM. Thus, these results suggest that healthy older adults who self-report greater levels of total physical activity exhibit enhanced descending pain modulatory function. Improved descending pain modulation may be a mechanism through which exercise reduces or prevents chronic pain symptoms.
CAREISM: USING SOCIOLOGICAL THEORY TO ANALYZE THE MATERIAL AND IDEOLOGICAL ROOTS OF THE U.S. CARE SYSTEM

Using Collins’ (2000) theory of power/inequality, we introduce the concept of “careism,” defined as (1) the unequal distribution of caregiver strain, (2) the bureaucratic incentive to view caregivers as functional tools instead of people, and (3) the devaluation of caregiving as a status, role, activity, and academic subject. Careism exists across all four of Collins’ power domains: structural, disciplinary, hegemonic, and interpersonal. These domains of power are important for understanding the demands and difficulties of caregiving and the maintenance of inequality in the U.S. care system. In addition to perpetuating injustice among those giving and receiving care, careism hinders caregiving research. Kleineman (2010) observes how caregiving lacks development as a crucial academic subject in which theory building is just as important as applied research. We outline dilemmas confronting the future of caregiving research due to this devaluation. Theorizing careism can reveal poorly understood mechanisms for inequality in caring systems, generate innovative solutions to the care crisis, and transform our care system and the ways that we care for one another.


WORDCOUNT: 205
PSYCHOLOGICAL PROFILES AND PAIN CHARACTERISTICS OF OLDER ADULTS WITH KNEE OSTEOARTHRITIS

Objective: The main objectives of the present study were to identify psychological profiles in persons with knee osteoarthritis (OA) and to determine the relationship between these profiles and specific pain and sensory characteristics including temporal summation and conditioned pain modulation. We hypothesized that: 1) specific psychological profiles would emerge based on responses across multiple psychological measures; 2) the profiles would significantly differ with respect to their reports of clinical pain and functional impact of their knee pain; and 3) these profiles would differ in their sensitivity to heat/mechanical pain, temporal summation and pain inhibition.

Methods: Older individuals with knee OA (n=194) completed psychological, health and quantitative sensory assessments. Hierarchical cluster analysis was used to derive psychological profiles that were compared across several clinical pain/disability and experimental pain responses.

Results: Cluster 1 had high optimism with low negative affect, pain vigilance, anger and depression along with the lowest self-reported pain/disability and the lowest sensitivity to mechanical, pressure and thermal pain (p’s<0.01). Cluster 2 had low positive affect with high somatic reactivity while Cluster 3 showed high pain vigilance with low optimism. Clusters 2 and 3 had intermediate levels of self-reported pain/disability and Cluster 3 experienced central sensitization to mechanical stimuli. Participants in Cluster 3 also displayed significant pain facilitation (p<0.05). Cluster 4 exhibited the highest pain vigilance, reactivity, negative affect, anger and depression. These individuals experienced the highest self-reported pain/disability including widespread pain (p’s<0.001). Cluster 4 was most sensitive to mechanical, pressure and thermal stimuli and showed significant central sensitization to mechanical and thermal stimuli (p’s<0.001).

Conclusion: Our findings demonstrate the existence of homogeneous psychological profiles displaying unique sets of clinical and somatosensory characteristics. Multidisciplinary treatment approaches consistent with the biopsychosocial model of pain should provide significant advantages if targeted to profiles such as those in our OA sample.
SALIVA AS AN ALTERNATIVE TO PLASMA TO MEASURE BIOMARKERS RELATED TO PAIN MECHANISMS: AGE-DIFFERENCES

Pain stimulation results in alterations to the functioning of the endocrine, immune and nervous systems which can be measured by relevant biomarkers. These biomarkers are typically studied in blood samples as proxies for the activation of specific neurobiological mechanisms in a person. A methodological concern is that the act of placing a central line/venipuncture for the collection of blood samples has been documented as a painful and stressful procedure that contaminates control sessions and potentially interacts with the experimental painful stimuli. A potential alternative is the collection of biomarkers through saliva samples. Saliva sampling is commonly used in studies of stress responses, however, it has not been established that biomarkers found in saliva correlate with biomarkers from blood samples relative to experimentally-induced pain. The use of saliva as a reliable substitute to blood would provide an avenue for biomarker measurement in large community-based pain studies that are otherwise not feasible (i.e., putting a central line in community-dwelling adults for repeated biomarker measurements). The current study delineated and quantified the standard basal and pain-evoked changes in saliva concentrations of a number of biomarkers and validated their analysis with plasma samples in the context of experimental pain stimulation. We characterized the time course, duration, and magnitude of changes in primary and secondary saliva and plasma biomarkers of interests in healthy older and younger adults using various experimental models of pain. Results provide novel information needed for future translational pain research.
THE ROLE OF FIRST GENERATION COLLEGE STUDENTS IN CARING FOR OLDER RELATIVES

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Abstract

First-generation college students (FGCS) have no family collegiate history and must overcome special challenges in adapting to the college environment. They also may have family responsibilities such as caring for older relatives. This paper compared the roles of FGCS and non-FGCS in caring for older relatives. 1445 college students at a large university completed an online survey; 34% were FGCS. Most FGCS were non-white (66%) and female (77%). Most students assisted in caring for relatives in some way. Care receivers were grandparents (68%), parents (24%), and other family members (8%). Students provided care everyday (4%), a few days/week (9%), a few days/month (26%), and a few times/year (60%). FGCS were significantly more likely than their peers to assist their older relatives in four of nine activities of daily living: dressing (P<0.0001), grooming (P<0.0001), oral care (P<0.001), and toileting (P<0.03). There were no significant differences in helping with bathing, feeding, transferring, walking, and climbing stairs (P>.05). FGCS were significantly more likely than their peers to assist their relatives in seven of eight general tasks: making medical appointments (P<0.0001), accompanying them to a medical appointment (P<0.002), helping to understand written materials (P<0.0001), acting as a translator (P<0.0001), filling out medical/insurance forms (P<0.0001), understanding medication usage (P<0.0001), and explaining medication side effects (P<0.0001). There was no significant difference in going online for health information (P>.05). Opportunities exist for colleges and universities to assist FGCS in balancing academics, college life, and family caregiving.
IMPROVED VERBAL LEARNING IN THE SEMANTIC VARIANT OF PRIMARY PROGRESSIVE APHASIA WHEN USING SEMANTIC CUES

Background / Objectives: The semantic variant of primary progressive aphasia (PPA-S) is characterized by impairments in confrontation naming and single word comprehension. Although episodic memory may be relatively spared, there can be significant impairment in verbal learning tasks. We report a patient with PPA-S who had impaired verbal learning but showed significant improvement in a verbal learning task when given semantic category cues.

Design/Methods: A 70 year old right handed woman with a 2 year history of progressive difficulties with word finding, naming, and memory was tested for language and memory deficits using the Hopkins Verbal Learning Test (HVLT). She was then retested on HVLT after being given semantic category cues.

Results: Confrontation naming was poor on the Boston Naming Test. Repetition was normal. Comprehension testing with word picture matching and sentence comprehension was normal. On a test of semantic associations, Pyramids and Palm Trees, she was impaired. She was also impaired on tests of verbal learning (HVLT) (total: 13) but not recall. When a different version of the HVLT was given with the semantic categories of the words given beforehand, her scores dramatically improved (total: 26).

Conclusions: This patient with PPA-S had an impairment of verbal learning, but not delayed recall. When given a semantic category cue beforehand, her verbal learning performance significantly improved. This observation suggests that this patient did not spontaneously use semantic encoding. Using a semantic cueing strategy may help other patients with PPA-S improve their capacity for verbal learning.
SELF VS. OTHER: BEHAVIORAL AND NEURAL EVIDENCE OF THE SELF-POSITIVITY EFFECT IN YOUNG AND OLDER ADULTS

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Abstract

Introduction. People typically view themselves as very positive when assigning attributes to themselves and when comparing the self with others ("self-positivity effect"). The majority of previous studies did not consider the age of the rater or the comparison group and collapsed across valence and content of rating dimensions. Based on evidence of processing differences as a function of age specificity and valence of information as well as developmental change in trait characteristics over the lifespan, two independent studies examined the effects of age (of rater and comparison group), positivity, and personality rating dimension on the self-positivity effect. In addition to behavioral evidence, neural processes involved in the self-positivity effect were explored.

Method. In Study 1, 27 young and 23 older participants rated 233 trait adjectives for age-typicality, self-typicality, and positivity for young and older others. In Study 2, 12 young and 12 older participants rated themselves and young and older others on the Big Five personality traits, while undergoing magnetic resonance imaging.

Result. Both studies provide support for a self-positivity effect. In Study 1, young, and particularly older, participants rated characteristics as more self-typical when they viewed them as more positive for their own-age group. In Study 2, the self-positivity effect varied across personality dimensions, with the effect present for conscientiousness and openness. This self-positivity effect was associated with greater anterior orbitofrontal cortex activity, an area associated with hedonic and reward processing. Results are discussed in the context of the better-than-average effect and self-serving biases and as reflecting identification vs. distancing from the own age group.
ATTITUDE DIFFERENCES AND PREPAREDNESS TO TAKE CARE OF THEIR OLDER RELATIVES AMONG COLLEGE STUDENTS.

The 2010 U.S. census revealed a rapidly growing population of older adults, and by 2050 predicted that the U.S population will include 88.5 million (more than 21 percent) over age 65. As more people live to the oldest ages, they suffer from multiple chronic conditions thus creating an extra ordinary demand for health care services. Due to the recent economic downturn and lack of professional caregivers the burden of care tends to fall on family including young college going adults. The dependency of aged individuals cultivates different attitudes among the young adults towards them and influence general care, and services they receive. Thus, it is essential to understand their attitude towards the older adults and their preparedness for the role of informal family caregivers.

Methods: A cross-sectional survey research method was used which included Caregiving Preparedness Scale (CPS), Refined Aging Semantic Differential scale (RASD) and, demographic profile information. Data from 350 university enrolled students was entered into SPSS and analyzed for descriptive and multivariate statistics.

Results and discussion: The study included majority females (69.6%), respondents who were juniors (33.6%) and identified themselves as white/Caucasian (56.2%). The RASD (chronbac’s α=0.975) and CPS (chronbac’s α= 0.908) yielded a high reliability among the college population. Mean scores reported a positive attitude of the students towards their older relatives (56.35±24.11, CI at 95%= 54.05-58.65) and other older adults (64.14±21.70, CI at 95%= 62.07-66.21) but the mean scores from CPS reported the students were not too well prepared (16.644±6.98, CI at 95%= 15.98-17.30) to take care of their older relatives in future. The results also suggests no statistical difference between the attitude towards older adults and their own older relatives (r= 0.660, p-value=0.000). The study concludes that students who were better prepared to take care of their older relatives had a more positive attitude towards them.

Conclusion/Implications: The results of the study indicate the lack of preparedness as informal caregivers among the students. This has implications for the geriatrics health care providers be informed about the attitudes and preparedness of young population and develop strategies to assist this particular group in taking better care of the older generation.

Submitted by: Gungeet Joshi, Ph.D candidate Department of Health Education and Behavior University of Florida.
ROLE OF MITOCHONDRIAL DNA REPAIR IN MUSCLE AGING

Sarcopenia is a human condition characterized by the progressive age-related decline in muscle mass, strength and functionality. Aging in muscle is characterized by high levels of apoptosis, by accumulation of oxidative damage, and by mitochondrial (mt) DNA abnormalities. These changes result in assembly of dysfunctional respiratory complexes and a progressive decrease in cellular availability of energy. These observations suggest that in aging muscle DNA repair pathways inefficiently remove DNA lesions from mitochondrial DNA (mtDNA).

We are investigating DNA repair pathways in aging muscle to identify molecular mechanisms underlying the age-related loss of muscle mass in sarcopenia. We hypothesize that a decline in muscular function with age is the result of reduced repair capacity in the aged muscle compared to the young. These changes may increase mtDNA instability, eventually causing activation of apoptotic pathways leading to muscle cell death. Towards this goal we are comparing efficiency of repair of oxidative DNA damage in nuclear and mitochondrial fractions from soleus and extensor digitorum longus muscle tissue isolated from young and old Fisher 344xBrown Norway rats.

Nuclear extracts and protein extracts from mitochondria are utilized as source of repair proteins and repair kinetics of base excision repair (BER) enzymes are carried out. The activities of individual BER enzymes are measured by incubating mitochondrial lysates or nuclear cell extracts with a radioactively-labeled oligonucleotide containing a single 8-oxoguanine modification, or an abasic site at a defined position. These substrates are used to specifically measure 8-oxoguanine DNA glycosylase activity and AP endonuclease activity. Repair activities are correlated with protein content in the corresponding fraction and evaluated in relation to muscle functionality in the aging rats.

Our studies for the first time will provide a comprehensive analysis of DNA repair and DNA maintenance mechanisms in an animal model system that most closely resembles the sarcopenia observed in humans. (Supported by NIA P30 AG028740).
Post-transcriptional regulation of gene expression has been demonstrated in yeast and mammalian embryonic stem cells by the technique of ribosome footprinting (RF). RF allows genome-wide quantification of levels of translation by deep-sequencing of mRNA fragments (footprints) protected from RNAse degradation by ribosomes during translation. We applied the technology to liver and muscle tissues from rat, obtaining in both cases useful amounts of ribosome footprints for library preparation and deep sequencing. The data collected from these experimental procedure will provide significant information on how aging affects processes of post-transcriptional control of translation.

We developed protocols to extend the RF technology to the analysis of translation in mammalian tissues. Muscle and liver tissue from Fisher 344xBrown Norway rats of different ages were dissected and rapidly flash-frozen in liquid nitrogen blocking translation elongation. Frozen tissue was subsequently pulverized without thawing. Cells were lysed in the presence of the translation-elongation inhibitor cycloheximide, RNA was digested with RNAse I and a monosome fraction collected through a resin column. RNA fragments of size 28-30 nt protected by the ribosome were size-selected and gel-eluted and purified from rRNA and tRNA contaminants using Ribo-Zero™ magnetic beads. Ribosome footprints 5’ and 3’ primed were reverse transcribed and PCR amplified to obtain final libraries ready to be sequenced with the Illumina Genome Sequencer.

The technique was applied to liver and muscle tissue disected from young rats. We successfully obtained RNA from the ribosome footprinted fraction of these tissues in amounts sufficient for the subsequent steps of library preparation and deep sequencing, as described in the protocol established in the RF procedure developed for yeast, mouse stem-cell cultures, and Escherichia coli. Hence, our results show that ribosome profiling can be successfully applied to mammalian tissues.

Application of ribosome footprinting to yeast and to mammalian embrionic stem-cells has revealed for the first time extensive post-transcriptional control of gene expression in response to oxidative stress. Thus, we expect that post-transcriptional control of translation will also be affected by the process of aging. The development and optimization of a ribosome profiling protocol applicable to aging mammalian tissue will provide a new tool to uncover unprecedented information on the relation between aging and protein synthesis.
GABAERGIC SIGNALING ALTERATIONS CONTRIBUTE TO IMPAIRED WORKING MEMORY IN AGED F344 RATS.

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Impairments in working memory functions supported by the prefrontal cortex (PFC) are a common feature of normal aging. Working memory critically involves GABAergic signaling in PFC; yet, surprisingly little is known about GABAergic alterations in PFC normal aging or whether such changes contribute to age-associated impairments in working memory. To investigate this, young adult (5 mo) and aged (25 mo) male F344 rats were characterized on an operant delayed response test of working memory in which rats must remember the location of a sample lever over a delay period (0-24 s) to obtain a food reward. Aged rats performed comparably to young at no delay but were impaired at long delays. After behavioral testing, western blotting was used to assess GABA signaling proteins in PFC homogenates. Immunoblots showed that the GABA synthesizing enzyme GAD67 was increased but the neuronal GABA transporter, GAT-1, was decreased in aged PFC. GABA(B) receptor (GABA(B)R) expression was also reduced in aged PFC. Among aged rats, expression of GAD and GAT-1 was not associated with working memory performance. In contrast, GABA(B)R expression was significantly and inversely associated with working memory such that lower GABA(B)R expression predicted better delayed response performance among aged rats. These data suggest that aging is accompanied by increased GABA availability within PFC and that downregulation of GABA(B)R expression may preserve appropriate levels of tonic inhibition required for optimal working memory. We next tested whether reducing GABA(B)R activation could improve working memory in aged rats. Young and aged rats received intraperitoneal injections of the GABA(B)R antagonist CGP55845 or vehicle prior to testing using a within-subjects design. Performance of aged rats was significantly improved by CGP55845. To determine if drug actions in PFC mediated this improvement, a cohort of young and aged rats received microinjections of CGP55845 or vehicle directly into medial PFC prior to testing. CGP55845 restored performance of aged rats to a level comparable to young adults. Together, these data indicate that age-related dysregulation of GABAergic signaling in PFC plays a causal role in impaired working memory in aging, and that targeting GABA(B)Rs provides therapeutic benefit for age-related impairments in working memory.
A BRIEF Olfactory TEST FOR ALZHEIMER'S DISEASE

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ABSTRACT

Background  The early diagnosis of Alzheimer’s disease (AD) may help reduce disability, enhance quality of life, and aid clinical trials. Portions of olfactory cortex are the initial sites of AD pathology and patients with AD often have more degeneration of their left than right hemisphere. Since the olfactory epithelium projects mainly to the ipsilateral olfactory cortex, patients with AD may demonstrate an asymmetrical (left greater than right) decrement of odor detection sensitivity. This retrospective, case-control study assessed a quick olfactory test that may help diagnose AD.

Methods  Participants with probable AD (N=18), mild cognitive impairment (MCI, N=24), other causes of dementia (OD, N=26) and matched controls (OC, N=26) were tested, with closed eyes, for their ability to detect an odor; one nostril at a time. A container of 14g of peanut butter was opened, held medially at the bottom of a 30 cm ruler, and moved up 1cm at a time during the participants’ exhale. Upon odor detection, the distance between the subject’s nostril and container was measured.

Results  The mean odor detection distance of AD patients’ left nostril (5.1 cm), and not their right (17.4 cm), was significantly less (F(3,90) = 22.28, p < 0.0001) than the other groups. The mean, standard error, and 95% Confidence Interval of the L – R nostril odor detection difference (cm) for AD were -12.4 ±0.5, (-15.0,-9.8); for MCI were -1.9 ±1.2, (-4.2,0.4); for OD were 4.8 ±1.0, (2.6,6.9); and for OC were 0.0 ±1.4 (-2.2,2.1).

Conclusion  This non-invasive and inexpensive left-right nostril odor detection test appears to be a sensitive and specific test for probable AD.
ONSET AND CHARACTERISTICS OF SPATIAL LEARNING IMPAIRMENT IN THE AGING FISHER × BROWN NORWAY F1 HYBRID RAT

Older age is an important risk factor for a variety of neuropsychiatric and neurodegenerative disorders, but even in the absence of pathology, aging is commonly associated with reductions in learning and memory. Fisher × Brown Norway (FBN) F1 rats are vigorous hybrids that age with low incidence of a variety of common pathologies; investigating learning and memory in such aged rats holds the potential to reveal important changes to cognition that can be ascribed to normal aging separate from confounds of disease or disorder. The current study evaluated spatial learning in male FBNF1 rats of 6 (n=93), 18 (n=22), 24 (n=144) or 28 (n=28) months of age with the goals of 1) profiling the temporal emergence of cognitive impairment in these hybrids and 2) clarifying the neuropsychological basis of age-related learning deficits. Analysis of performance on a multi-day place learning (Morris water maze) protocol revealed learning impairment emerges at middle-age (18 mo) and continues into advanced ages (24-28 mo), although there was considerable variation among individuals of all ages. Differences in spatial learning were due to impaired acquisition, not defective recall, as older rats were less efficient at learning within a day of training but all age groups demonstrated comparable retention between days of training. Furthermore, impaired learning in older rats was not due to unstable trial-to-trial performance as within-subject variability was not different with age; group differences were selectively attributed to a subset of aged rats that never employed a spatially guided search despite continued training while other aged rats did utilize a spatial strategy, an approach typical of cognitively intact young adults (6 mo). These data reveal that cognitive decline is an ongoing, though not an inevitable, feature of normal aging. Importantly, these changes to cognition are due to impaired acquisition of information, not deficient retention, and individual differences are highly reliable within and between groups of various ages. These data elucidate features of translational relevance to human neurocognitive aging as findings in controlled studies of healthy, older humans suggest symptoms of forgetfulness or unstable cognitive performance likely signal incipient neurological illness, not normal aging.
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A CASE SERIES OF TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR TREATMENT RESISTANT GERIATRIC DEPRESSION

Introduction: Depression occurs in approximately 15% of the geriatric population with approximately 3% meeting criteria for a major depressive episode in the general population and up to 25% in primary care and nursing home settings. The effects of depression on an individual are widespread and include the loss of enjoyment, loss of functioning, increase in medical conditions, and increase in mortality. Antidepressant medications are effective in only 50-60% of cases and possess many side effects and precipitate many drug-drug interactions. Treatment resistant depression can be defined as the failure of one antidepressant medication. The likelihood of a response with an antidepressant significantly decreases with each failed attempt. Depression is hypothesized to result from dysfunction of fronto-limbic brain circuitry. Functional imaging studies have demonstrated hypoactivity of the left prefrontal cortex in depressed patients. TMS is able to enhance the activity of the prefrontal cortex by utilizing a pulsed magnetic field to create an electrical current by Faraday’s Law. TMS was approved by the FDA to treat depression in October, 2008. TMS possesses no systemic side effects and has no drug interactions and is a potential ideal treatment option in geriatric patients.

Objective: The objective of this case series is to determine the effectiveness and side effect profile of TMS in geriatric treatment resistant depression.

Methods: I treated 14 patients in a treatment resistant major depressive episode with TMS using the FDA approved protocol. The Montgomery Asberg Depression Rating Scale (MADRS) was utilized to measure the severity and change in depressive symptoms. It was completed prior to treatment and weekly throughout treatment. Side effects were assessed daily by interview.

Results: 78.6% patients achieved a greater than 50% reducted in symptoms with 42.9% achieving remission of their depression. Patients averaged a 61.6% reduction in symptoms. No patients stopped treatment do to side effects and the only side effect reported was mild scalp discomfort.

Conclusions: TMS demonstrated effectiveness and minimal side effects in treatment resistant depressed geriatric patients. The results of this case series suggest TMS is an effective, well tolerated option for treatment resistant geriatric patients.
Triptolide inhibited telomerase activity and shorten telomere in human tumor cell contributed to tumor cell aging

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BACKGROUND:

While most somatic cells express only low levels of telomerase, it is significantly upregulated in most of human tumors. Indeed, one of the characteristics of tumor cells is the stabilization of the telomeres by constitutive expression of telomerase activity. Thus, one promising approach to cancer therapy is targeting the telomerase. We examined triptolide (TPL), with regard to its effects on telomerase activity and telomere length in human TSU bladder cancer cells and MDA-435s breast cancer cells

METHODS:

Telomerase activity of TSU and MDA-435s cells was measured by the TRAP assay. Telomerase length was measured using PNA-FACS method. The hTERT in telomerase complex was assayed by western blot. The cell cycle of two cell line was assayed by FACS. Two cancer cells treated with TPL in low concentration and stained with β-galactosidase were calculated.

RESULTS:

When TSU and MDA-435s cells treated with TPL, their telomerase activity showed significantly lower in doses dependent as compared with vehicle alone. The hTERT in these cell treated with TPL was significantly reduced as compared to vehicle alone. Furthermore, these cells treated with TPL (0.5ng/ml, 1ng/ml or 10ng/ml, 15ng/ml) more than 30 -35 days resulted in a significant shorting of the telomeres assayed by PNA- flow cytometry as comparing with vehicle alone. Cell cycle in these cells treated with TPL showed blocking in the G1 phase. In addition, the doubling time of two cell lines treated with TPL increased more than two times as comparing with vehicle alone. Positive stained β-galactosidase cells in TSU and MDA-435s cells treated with TPL for 35days significantly increased 91% and 97% more than that of vehicle alone respectively.

CONCLUSIONS:

This is the first study on telomere and telomerase activity in aging cancer cells treated with Triptolide. Low doses of TPL can inhibit hTERT expression and telomerase activity, shorten the telomeres, block cell cycle progression and promote the entry of tumor cell into a senescent state. These properties may be partially responsible for the anti-tumor activity of TPL.
Triptolide inhibited telomerase activity and shorten telomere in human tumor cell contributed to tumor cell aging

*Cytometry*. 2002 Nov 1;49(3):96-105.

**Simultaneous flow cytometric analysis of two cell surface markers, telomere length, and DNA content.**

Schmid I, Dagarag MD, Hausner MA, Matud JL, Just T, Effros RB, Jamieson BD.

Source

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**Improved procedure for the measurement of telomere length in whole cells by PNA probe and flow cytometry.**

Carbonari M, Mancaniello D, Cibati M, Catizone A, Fiorilli M.

Source

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AGING DEPRESSES PROTECTIVE IMMUNITY AND PROLONGS INFLAMMATION IN SEVERE BLUNT TRAUMA SUBJECTS


INTRODUCTION: Exacerbated morbidity and mortality in the elderly after severe trauma (ST) may be secondary to either ‘hyperinflammation’ or ‘immuno-senescence’. The goal of this study was to determine whether the elderly have unique genomic patterns in neutrophils in the acute/subacute periods after ST consistent with either response.

METHODS: Microarray data collected in the Glue Grant from 34 severely traumatized adult patients were used to evaluate genome-wide expression from blood neutrophils on days 0.5, 1, 4, 7, 14, and 21 after ST. 17 elderly (≥55yo) and young (<55yo) patients with complicated ICU outcomes were matched based on gender and AIS score for comparison to non-injured controls (n=17). Subsequent analysis consisted of identifying differences in gene expression (p<0.001), individual fold gene changes (vs. control, p<0.05), gene ontologies, as well as functional pathways among elderly and young ST patients, and healthy subjects.

RESULTS: In the young, genome-wide expression patterns at 0.5 and 7 days were significantly more aberrant from control subjects than those in the elderly. Among 61 genes whose dysregulation is known to predict complicated outcomes after ST in young patients (CCM 2013 41(5):1175-85), we found that the aberrant genome expression was significantly less in the elderly populations at 0.5 and 1 days, and greater at 4 days. Fold changes in genes involved in inflammation, myeloid derived suppressor cells, and chemotaxis were also increased from control more in the young than the elderly at 0.5 days (Z>2.0). By day 4, young patients’ gene expression patterns appeared to return to baseline, while the dysregulated expression of the elderly patients persisted. The top canonical pathways involved in innate immunity in the young compared to elderly were significantly upregulated at 0.5 days and then downregulated by day 4.

CONCLUSION: Our findings reveal a unique early genomic expression pattern of elderly patients after ST consistent with ‘immuno-senescence’. Initially, there is a diminished immune response compared to their younger counterparts, followed by prolonged up regulation of inflammatory genes associated with ‘hyperinflammation’. This research indicates that interventions to improve outcomes in the elderly will need to be distinct from younger cohorts, and address multiple components of protective immunity.
Wang, Jin-Hee (Surgery); Ahn, In-Sook (Surgery); Fischer, Trevan (Surgery); Byeon, Jae-Il (Surgery); Dunn, Jr, William A. (Anatomy & Cell Biology); Behrns, Kevin E. (Surgery); Leeuwenburgh, Christiaan (Aging & Geriatric Research, Institute on Aging); Kim, Jae-Sung (Surgery, Pharmacology & Therapeutics, Institute on Aging).

IMPAIRED MITOPHAGY AFTER ISCHEMIA/REPERFUSION OF AGED MOUSE LIVERS

Purpose/Background: Mitochondrial dysfunction is the penultimate event of ischemia/reperfusion (I/R) injury. Aged livers have significantly less reparative capacity following I/R injury. Mitophagy is a catabolic process that selectively targets and clears damaged or abnormal mitochondria. We have shown that enhancing mitophagy ameliorates hepatic I/R injury to young livers (Hepatology, 2008:47, 1725). However, it is unknown how mitophagy affects I/R injury to aged livers.

Methods: Hepatocytes and whole livers from 3 and 26 month old mice were subjected to simulated and in vivo I/R, respectively. Cell death was assessed by propidium iodide (PI) fluorometry. Changes in autophagy-related proteins (Atg) were analyzed by immunoblotting. To modulate specific Atg levels, hepatocytes and livers were treated with adenoviral vectors expressing Atg4B or Beclin-1. The mitochondrial membrane potential, mitochondrial permeability transitions (MPT), onset of mitophagy and cell death were assessed by confocal microscopy. Changes in mitochondrial membrane potential and autophagy in vivo were monitored by intravital multiphoton microscopy.

Results: Aged hepatocytes rapidly underwent the MPT-dependent I/R injury. Immunoblotting analysis demonstrated that reperfusion of aged cells activates calpain 2, which in turn depletes Atg4B and impairs mitophagy. Blockage of Atg4B depletion or overexpression of Beclin-1 recovered the autophagic flux and mitophagy, prevented onset of the MPT, and suppressed cell death after reperfusion. Immunoprecipitation assay revealed a novel interaction of Beclin-1 with Atg3, a central protein for autophagosome formation and mitochondrial homeostasis. Critical roles of Atg4B and Beclin-1 in I/R injury to aged livers in vivo were confirmed with immunoblotting, genetic and multiphoton imaging analysis.

Conclusions: Impaired mitophagy resulting from calpain activation and subsequent Atg4B loss contributes to the age-dependent sensitivity to I/R injury. Enhancing mitophagy could be a novel therapeutic strategy to improve liver function in elderly patients after liver resection or transplantation surgery.
A FAILURE TO RESOLVE INFLAMMATION RATHER THAN HYPER-INFLAMMATION CHARACTERIZES THE AGED RESPONSE TO SEVERE TRAUMA

Objectives: It is well established that the elderly have worse outcomes after trauma, including increased infections. Using a recently described murine polytrauma (PT) model, we compared the leukocyte responses of old and young mice after injury, as well as their survival to subsequent *Pseudomonas* pneumonia (*Pp*). Methods: 6-10 wo young and 18-24 mo old B6 mice underwent 90 minutes of shock (MAP 30 mmHg) and resuscitation via femoral artery cannulation, followed by laparotomy with cecetomy and femur fracture + muscle tissue damage. Mice were euthanized 2 hours (2h), one day (1d) and three days (3d) after PT and their spleens, bone marrow, blood and serum were collected; leukocyte phenotypic and functional analysis were performed. Genome-wide expression was performed on total blood leukocytes. Expression patterns were compared between healthy and young/old PT mice at p<0.001 (F test). Intranasal *Pseudomonas* was instilled to induce *Pp* 1d post PT. Results: Serum cytokine/chemokine concentrations were not different between young and old mice and there were few differences in the numbers and activation/functional status of bone marrow, spleen and blood leukocytes. However, the blood WBC transcriptomic response to PT differed markedly in young and aged mice (p<0.05). Old and young mouse showed similar overall transcriptomic changes at 2h, but old mice did not show early increased up-regulation of genes related to PMN-mediated immunity, chemokine/chemokine receptor binding and responses to pathogen-associated molecular patterns. At 1d, the transcriptome from young mice returned to baseline, whereas a similar return was not seen in aged mice even at 3d. Finally, aged PT mice given *Pp* at 1d had a significantly increased mortality (55%; p<0.02 vs naïve, *Pp*, young PT+*Pp*). Conclusion: Although 'inflamma-aging' exists, it’s role in increased infections and mortality after trauma in the aged is modest. Rather, a failure of leukocytes from the aged to initiate an early innate immune response, and a subsequent inability to effectively resolve their inflammatory response to severe injury may leave them at risk to subsequent infection. A proper understanding of this phenomenon is critical to improving elderly patient outcomes in the future.
Inflammation, an important component associated with the progression of stroke and excitotoxicity-mediated brain damage, is partially mediated by cyclooxygenase (COX)-1 and -2 enzymes and its downstream prostaglandins. With the side effects associated with COX-2 inhibitors, focus has been shifted towards the role of prostaglandins (PGD$_2$, PGE$_2$, PGI$_2$, PGF$_{2\alpha}$, and TxA$_2$) and their receptors as therapeutic targets in minimizing neurologic conditions. PGD$_2$ is the most abundant prostaglandin in the brain and plays a vital role in various physiological and pathological conditions; however, its role in excitotoxicity and stroke is elusive. We tested the hypothesis that PGD$_2$ DP1 receptor is neuroprotective in transient cerebral ischemia and in NMDA-induced acute excitotoxicity. Ischemia-reperfusion injury in WT and DP1$^{-/-}$ was induced by a transient 90min middle cerebral artery occlusion (MCAO) followed by 4d reperfusion. The resulting infarct size was 49.0% larger in DP1$^{-/-}$ mice ($p<0.01$) than in WT mice. Since excitotoxicity is an important mediator of stroke, we further tested our hypothesis in NMDA-induced excitotoxicity model. DP1$^{-/-}$ mice injected with 15nmol NMDA had 24.6% greater lesion volume than did the WT mice ($p<0.05$). Furthermore, to test whether pharmacological activation of DP1 receptor by selective agonist will have neuroprotective effect; mice were given an intracerebroventricular (ICV) injection of the DP1 receptor-selective agonist BW245C or vehicle. Twenty minutes later, 15nmol NMDA was injected stereotactically into the striatum. After 48h, analysis of the cresyl violet-stained brain sections revealed significant attenuation in lesion volume by 23.7%, 43.8%, and 33.9% for 10, 25, and 50nmol BW245C, respectively. To test whether the minimum effective dose obtained in NMDA-induced toxicity is equally effective against MCAO, mice were given 10nmol BW245C ICV followed by 90min MCAO and 4d-reperfusion. BW245C significantly attenuated the infarction volume by 21.0% ($p<0.05$). Interestingly the NMDA-induced brain damage was also aggravated in aged (16-month-old) DP1$^{-/-}$ mice ($p<0.05$) as compared with age-matched WT mice. These are the first set of studies demonstrating that the DP1 receptor is neuroprotective. In conclusion, DP1 receptors are vital in minimizing brain damage and could be considered as a potential adjunct therapeutic tool against various acute neurological conditions in both young and aged population.
**Metabolic rate of walking in fatigued vs. non-fatigued Older Adults**  
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Key words: Aging, Fatigue, Cost of Walking, Energy Expenditure, Walking Economy

Introduction. Older adults who report fatigue, tiredness or exhaustion are at elevated risk for death and functional impairments. This study evaluated the metabolic rate of walking in severely fatigued compared to non-fatigued older adults in an effort to explain fatigue symptoms.

Methods. We conducted a case-control study of older adults who reported severe fatigue (N=20, 70.8±4.9 yrs) and controls without fatigue (N = 25; 73.2±5.0 yrs). Individuals with overt medical conditions and other common reasons for fatigue symptoms (e.g. thyroid levels) were excluded from the study. Participants walked on a treadmill at a standard pace of 40.2 m/min and at a preferred walking speed (range: 48 - 83 m/min) for 5 minutes each. Gross, mass-specific and mass-specific net metabolic rate of walking were determined using indirect calorimetry. Measures of perceived exertion were also assessed while walking.

Results. Gross metabolic rate of walking at a standard pace was similar between fatigued (285±92 watts) and non-fatigued (303±69 watts) participants (p=0.48). No group differences were found with mass-specific (Fatigued: 3.8±0.94 vs. Not-fatigued: 3.7±0.67 watts, p=0.59) and mass specific net metabolic rate (Fatigued: 2.5±0.92 vs. Not-fatigued: 2.5±0.56 watts, p=0.87). No group differences were seen at a preferred walking pace in all measures of walking metabolic rate. Fatigued participants rated their perceived exertion similar to non-fatigued participants.

Conclusions. Metabolic rate of walking in older adults who report severe fatigue was similar to those who do not report fatigue. Reports of fatigue in elders are unlikely to be explained by a higher metabolic rate of movement.
**TITLE:** CHRONIC RESVERATROL SUPPLEMENTATION AND BRAIN OXYGENATION: A PILOT STUDY

**Background:** Kennedy et al. (2010) showed acute effects of Resveratrol, a phytoalexin polyphenol common in grape products (e.g. red wine), on neurodegenerative functions and brain blood oxygen concentration.

**Purpose:** The purpose of this study was to evaluate chronic effects resveratrol supplementation frontal lobe hemoglobin concentrations using near infrared spectroscopy.

**Methods:** This randomized, double-blind, placebo-controlled pilot study included men (N=12 (54.54%)) and women between the ages of 65 and 100 (73.34 ± 7.02). Overweight or obese, non-smoking, sedentary individuals who were not on cholesterol medication and did not consume wine on a regular basis were randomized to receive placebo (N =7), 300 mg (N =9), and 1000 mg (N =6) of resveratrol for 90 days. The participants performed cognitive tests while bilateral side frontal lobe hemoglobin concentrations were collected using near-infrared Spectroscopy that calculated oxygenated hemoglobin (OxHb), deoxygenated hemoglobin (HHb), total hemoglobin (TotHb) and tissue oxygen index (TOI). All concentrations were normalized to a resting condition.

**Results:** In this small sample of participants, resveratrol supplementation did not significantly alter hemoglobin concentration as compared to placebo. However, there were some trends that indicate that resveratrol increased OxHb and TotHb concentration. As compared to placebo, participants randomized to 300 mg and 1000 mg of resveratrol had a 1.5 µmol/l (p = 0.374) and .94 µmol/l (p = 0.605) increase in oxyhemoglobin concentration on the right side, respectively. Right side TOI among participants taking 250 mg and 1000 mg of resveratrol showed an increase of 2.09% (p = 0.178) and 2.14% (p = 0.252) respectively. Similar results were found on the left side.

**Conclusion:** Despite non-statistically significant effects, this pilot study demonstrates that chronic resveratrol supplementation might lead to greater frontal lobe oxygenated hemoglobin concentration. Results will serve to plan for a future study with an adequate sample size to detect alterations in brain hemoglobin concentration following resveratrol supplementation.
THE LEUKOCYTE TRANSCRIPTOME CAN EXPLAIN IMMUNE SUPPRESSION AND DEFECTS IN THE NEONATAL AND ELDERLY IMMUNE RESPONSE TO SEPSIS

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Introduction: Populations encompassing extremes of age, including neonates and elderly, have greater mortality from sepsis. We propose that transcriptomic differences in whole blood leukocytes provide global insights into mechanisms behind the increased mortality observed in neonatal and elderly populations.

Methods: Neonatal (5-7 days), young adult (6-12 weeks), and elderly (20-24 months) mice underwent cecal slurry model of intra-abdominal sepsis and white blood cells for RNA isolation were collected at 2 hours, 1 and 3 days following sepsis. Genome-wide expression and functional analysis was performed and expression patterns were compared at p<0.001.

Results: Healthy neonatal mice had significant differences in baseline gene expression patterns compared to adult and elderly mice as determined by leave-one-out cross validation (p<0.001). Elderly and neonatal mice both had increased mortality to sepsis compared to young adult mice with the same insult (P<0.001). There were 7,012, 4,990, and 7,479 unique genes that were differentially expressed by the three groups at 2 hours, 1 day, and 3 days (p<0.001). When examining the neonatal response to sepsis over time compared to the adult response, neonatal mice only upregulate a very small portion of their genome compared to adult mice. Likewise, neonates have only 884 unique genes that are significantly altered following sepsis compared to greater than 4893 and 4520 unique genes which are changed in the young adult and elderly populations (p<0.001). Both neonatal and elderly transcriptomic responses to sepsis were markedly attenuated or even down-regulated compared to young adult mice (p<0.001) early after sepsis, and elderly mice have a persistent response with failure to return to baseline by three days.

Conclusions: This study reveals that the neonatal transcriptome is distinct from the adult transcriptome not only at baseline, where adaptive immune gene expression is suppressed, but also in response to polymicrobial sepsis where their innate immune responses are markedly attenuated. Elderly mice also exhibit a dysfunctional response to sepsis, characterized by attenuated innate inflammatory response with continued systemic inflammation and adaptive immune suppression, with the inability to return toward baseline homeostasis. Additionally, neonatal and elderly mice have profoundly different responses to sepsis, although the net result of increased mortality is similar.
Objective
This study investigated how race and verbal prompting interact with age to predict longitudinal age-trajectories on a performance-based measure of everyday cognition.

Participants and Methods
African American (n=727) and Caucasian (n=2052) older adults from the ACTIVE clinical trial were followed for up to ten years (mean baseline age=74.21 years; mean education=13.52 years). Participants were given the Observed Tasks of Daily Living (OTDL; an objective measure with tasks involving medication management/finances/telephone use) at baseline and at 1-, 2-, 3-, 5-, and 10-year follow-ups. When participants said “I don’t know” or did not respond to an item, they received a standardized verbal prompt. The prompts were not designed to give the answer, but only to serve as motivation or cue to initiate the first step. At each occasion, unprompted (sum of items correct without prompting) and prompted (sum of items correct including both prompted and unprompted) scores were derived for each participant. Multi-level modeling, adjusting for demographics/health/training group, was used to determine the linear and quadratic age-trajectories of OTDL performance by race.

Results
When vocabulary (a proxy for quality of education) was included as a covariate, the race main-effect on OTDL performance became non-significant. There were significant main effects of linear-age, quadratic-age and prompting. Two- and three-way interactions were significant such that for the unprompted condition, compared to Caucasians, African Americans demonstrated an accelerated (quadratic) decline in OTDL performance beginning at about 80 years-old. The prompted condition, however, did not demonstrate differential rates of age-related change between African American and Caucasian participants. There were also significant between-individual differences in rates of age-related change.

Conclusions
While there was accelerated decline for the unprompted OTDL performance in African Americans as they transitioned into old-old age, minimal prompting appeared to eliminate these differential trajectories between African Americans and Caucasians on a measure of everyday cognition. These findings may have implications for simple prompting during neuropsychological assessment in the old-old. Future work will attempt to identify mediators of the accelerated decline in everyday cognition observed in older African Americans.